

**REMARKS**

Claims 1, 2, 6 and 9-16 are all the claims pending in the application.

Claims 9-15 are withdrawn as directed to a non-elected invention. Claims 1, 2 and 6 are being examined and are rejected.

Claim 1 is amended to delete certain members of a Markush group and to recite the 6-membered heteroaryl is pyridyl as supported at least at page 16, lines 6-10. The definition of Y in claim 2 is amended in view of the amendment to claim 1. The dependencies of claims 6, 9, and 14-16 are amended in view of the cancellation of claims 3 and 5.

No new matter is added and entry of the amendment is requested, respectfully.

**I. Claim to Priority**

The Examiner is requested, respectfully to acknowledge Applicants' claim to priority and receipt of the priority document on February 1, 2005, as indicated in PAIR.

**II. Detailed Action**

**A. Claim Rejections - 35 U.S.C. § 112**

Claims 1-3, 5 and 6 remain rejected under 35 U.S.C. § 112, first paragraph as lacking enablement for the full scope of the claims. The Examiner admits that the specification is enabling for compounds where R<sup>2</sup> is phenyl, pyridyl, furan, or C≡C-alkyl, and compounds as given in table 1. However, the Examiner asserts that the specification does not enable compounds where R<sup>2</sup> is any heterocyclic group.

This rejection is overcome by amending claim 1 to recite the 6-membered heteroaryl is pyridyl. Accordingly, the Examiner is requested, respectfully, to reconsider and remove this rejection.

**B. Claim Rejections - 35 U.S.C. § 103 and Obviousness-type Double Patenting**

The rejection under 35 USC § 103 as being obvious over WO 01/27086 Hanada and also the Double Patenting rejection over US 7,037,919 still stand. According to the Examiner, the unexpected results are drawn to only one compound. However, the Examiner asserts that the cited references have several substituted phenyls and Applicants have not shown unexpected results for those compounds.

For the following reasons, the rejections are traversed and/or overcome, respectfully.

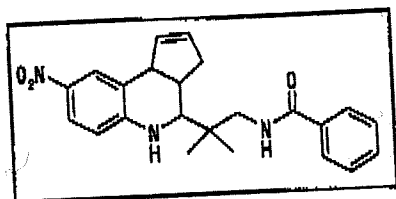
**1. Rejection under 35 USC § 103 as being obvious over WO 01/27086 Hanada**

In order to further differentiate the compounds of the present invention from the compounds disclosed in Hanada et al., claim 1 has been amended to recite that R<sup>1</sup> is a cyano group and that Y is -NR<sup>3</sup>CO-.

Thus, the compounds claimed in the present application are characterized in that the ring condensed with the tetrahydroquinoline moiety is saturated; R<sup>1</sup> is a cyano group; Y is -NR<sup>3</sup>CO-; and R<sup>2</sup> is a phenyl group having R<sup>4</sup> at 4-position or a pyridyl group having R<sup>4</sup> at 4-position, wherein R<sup>3</sup>, R<sup>4</sup> and R<sup>4'</sup> are as defined in amended claim 1. The compounds claimed in the present application do not exhibit excessive action on the prostate, but exhibit strong androgen receptor agonistic action, particularly on bone tissue and skeletal muscle tissue (See Test Examples in the specification).

On the other hand, WO 01/27086 discloses compounds which cover a broad scope of structurally divergent compounds. However, all the species disclosed have the ring condensed with the tetrahydroquinoline moiety and unsaturated with a double bond. In addition, almost all the species disclosed have a nitro group as a substituent that corresponds to  $R^1$  of the present compounds. WO 01/27086 does not disclose any specific compounds that have a cyano group as a substituent that corresponds to  $R^1$ ;  $-NR^3CO-$  as a substituent that corresponds to Y; or a substituted phenyl or pyridyl group as a substituent that corresponds to  $R^2$ . WO 01/27086 neither teaches nor suggests the compounds claimed in the present application which have the characteristic structure as explained above.

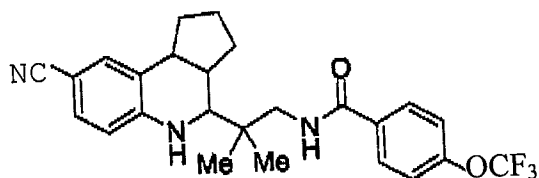
In order to prove that the compounds claimed in the present application have unexpected androgen receptor agonistic action over WO 01/27086, Applicants previously submitted a Rule 132 Declaration which shows the androgen receptor agonistic action of the compound of Example 56 in WO 01/27086, which is represented by the following formula:



The Examiner has pointed out that some compounds disclosed in WO 01/27086 have a substituted phenyl as a substituent that corresponds to  $R^2$ . However, the compounds of WO 01/27086 also have  $-NHSO_2-$  as a substituent that corresponds to Y. Therefore, in the Rule 132 Declaration, the compound of Example 56 which has  $-NR^3CO-$  as a substituent corresponding to

Y was selected as a compound which was structurally the closest to the compounds claimed in the present application.

The present specification shows in Test Example 2 that the compound of Example 1:



exhibited no excessive action on the prostate but exhibited a strong androgen receptor agonistic action on levator ani muscle and bone mineral density (See Table 4 below).

Table 4

Test compound	Prostate weight (mg/100 g body weight)	Femoral bone mineral density (mg/cm <sup>2</sup> )	Levator ani muscle weight (mg/100g body weight)
Sham control group	94±17	140±6	53±4
ORX control group	8t1	128±4	35±4
ORX+Example 1 30 mg/kg	70±13**	137t10**	60±6**

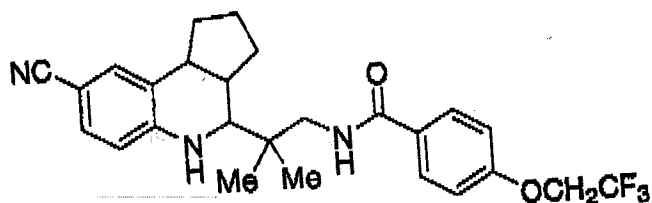
Mean±SD      \* $p < 0.05$ , \*\* $p < 0.01$  on Dunnett's *t* - t e s t .

In the Rule 132 Declaration, the same experiment as in Test Example 2 of the specification was conducted except that the compound of Example 56 in WO 01/27086 was used in an amount of 60 mg/kg, which is twice as much as that of the compound of Example 1.

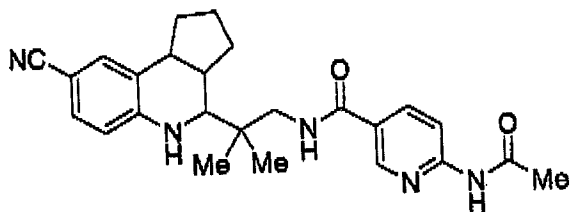
As shown in the Figures attached to the Declaration, the compound of Example 56 in WO 01/27086 did not show any significant androgen receptor agonistic action on bone mineral density even in an amount of 60 mg/kg.

The present specification also shows in Test Examples 3 and 4 that the compound of Examples 8, 23 and 16 has no excessive action on the prostate, but exhibited a strong androgen receptor agonistic action on levator ani muscle and bone mineral density (See Tables 5 and 6 below).

Ex 8



Ex 23



Ex 16

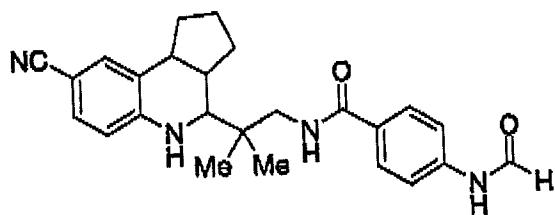


Table 5

Test compound	Prostate weight (mg/100 g body weight)	Femoral bone mineral density (mg/cm <sup>2</sup> )	Levator ani muscle weight (mg/100 g body weight)
Sham control group	123±17	140±5	60±4
O R X control group	8±2	131±6	38±4
ORX+Example 8 30 mg/kg	62±10**	136±3**	58±6**
ORX+Example 23 30 mg/kg	111±14**	137±5**	72±6**

Mean±SD \* $p < 0.05$ , \*\* $p < 0.01$  on Dunnett's  $t$ -test.

Table 6 (in the case of oral administration)

Test compound	Prostate weight (mg/100 g body weight)	Femoral bone mineral density (mg/cm <sup>2</sup> )	Levator ani muscle (mg/100 g body weight)
Sham control group	111±14**	140±4	55±5
ORX control group	8±4	132±6	34±4
ORX+Example 16 30 mg/kg	90±24**	136±10**	60±6**

Mean±SD \* $p < 0.05$ , \*\* $p < 0.01$  on Dunnett's  $t$ -test.

Therefore, it is unexpected from WO 01/27086 that the claimed compounds of the present application exhibit a strong androgen receptor agonistic action on levator ani muscle and bone mineral density even when they are used in an amount of half the amount of the compound of Example 56 in WO 01/27086.

In conclusion, WO 01/27086 neither teaches nor suggests the characteristic structure of the compounds claimed in the present application. In addition, the compounds claimed in the present application have unexpected effects as compared to the compounds disclosed in WO 01/27086 and thus, are unobvious from WO 01/27086.

**2. Obviousness-type double patenting rejection**

This rejection is overcome by the amendments to the claims.

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

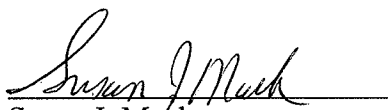
Respectfully submitted,

SUGHRUE MION, PLLC  
Telephone: (202) 293-7060  
Facsimile: (202) 293-7860

WASHINGTON OFFICE

**23373**

CUSTOMER NUMBER

  
Susan J. Mack  
Registration No. 30,951

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